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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER
EPPS, JANET L

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1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/851,871	Applicant(s) BENNETT ET AL.
	Examiner Janet L. Epps-Ford, Ph.D.	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: Page 96 (for example) of the specification as filed refers to a Figure 11, however it is noted that only Figures 1-10 were submitted by Applicants.

Appropriate correction is required.

2. The use of the trademarks, for example, OptiMEM™ and Lipofectin™, page 73, lines 13-14, have been noted in this application. The reference to the trademark should be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks (See MPEP § 608.01(v)).

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-38 and 51-62 of U.S. Patent No. 6,319,906, and over claims 1-18, and 20-37 of US Patent No. 6,077,833. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-14 of the instant application that are drawn to a method for treating an inflammatory skin disorder comprising topically applying an antisense compound targeted to a nucleic acid molecule encoding a human B7 protein to an individual are an obvious variation of claims 1-38 and 51-62 of US Patent No. 6,319,906 (US'906) and claims 1-18 and 20-37 of US Patent No. 6,077,833 (US'833). The claims of US'906 are drawn to antisense compounds, pharmaceutical compositions comprising said antisense compounds and an anti-inflammatory or immunosuppressive agent, methods of modulating the expression of a human B7 protein in cells or tissues comprising contacting cells or tissues with said antisense compounds, and methods of treating an inflammatory disease or condition in an animal comprising administering co-administering antisense compounds targeting nucleic acid encoding human B7-1 and B7-2 proteins. The claims of US'906 also recite antisense oligonucleotides comprising modified nucleobases, sugar moieties, and covalent linkages. The claims of US'833 are drawn to antisense compounds targeting human B7-1 or human B7-2, pharmaceutical compositions comprising these antisense compounds, and methods of modulating the expression of human B7-2 or human B7-1 in cells of tissues comprising administering antisense oligonucleotides targeting the nucleic acid encoding human B7-1 or B7-2.

The claims of the instant application differ from the claims of the issued US Patents to the extent that the claims of the issued patents do not specifically recite a method for treating an

inflammatory skin disorder such as psoriasis, contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular dermatitis, generalized exfoliative dermatitis, or eczema, and wherein the above antisense compounds or compositions are administered topically to a patient. However, the claims of the instant application that recite the various inflammatory skin disorders mentioned above are an obvious variation of the claims of the issued US Patents. For example, the disclosure of both US'906 and US'833 (bridging paragraph of col. 3-4) state that "there is a long-felt need for compounds and methods which effectively modulate critical co-stimulatory molecules such as the B7 proteins. It is anticipated that oligonucleotides capable of modulating the expression of B7 proteins provide for a novel therapeutic class of anti-inflammatory agents with activity towards a variety of inflammatory or autoimmune diseases, or disorders or diseases with an inflammatory component such as.... psoriasis, contact dermatitis, rhinitis and various allergies." The disclosure of the issued US Patents clearly provide specific motivation for modifying the issued claims to recite a method for treating inflammatory skin disorders such as psoriasis or dermatitis in an animal, since these conditions are expressly set forth in the disclosure of US'906 and US'833 as alternate embodiments of the claimed invention (bridging paragraph of col. 3-4).

Moreover, the claims of the issued US Patents do not recite the formulation or lipophilic moiety recited in claims 11-12 of the instant application. However, again, the formulation and lipophilic moiety are also obvious variations of the issued US Patents since they are disclosed as alternative preferred embodiments of these inventions. For example, the disclosure of US'906 (col. 14, lines 51-53) and US'833 (col. 14, lines 26-28) both recite "[F]ormulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops,

suppositories, sprays, liquids and powders." In regards to the lipophilic moiety of claim 12, US'906 (col. 10, lines 9-13) and US'833 (col. 9, lines 59-63) both recite "[A]nother preferred additional or alternative modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more lipophilic moieties which enhance the cellular uptake of the oligonucleotide."

Therefore, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the claimed methods recited in issued US Patents US'906 and US'833 to recite the method for treating an inflammatory skin disorder as per the instant invention. One of ordinary skill in the art at the time of filing would have been motivated to make this modification since the disclosure of both US'906 and US'833 disclose the instantly claimed method and antisense compounds as alternative preferred embodiments of the claimed invention of these issued patents.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 6, and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Stinchcomb et al. (US 5,877,021).

Claim 1 recites a method for treating an inflammatory skin disorder in an individual in need thereof, comprising topically applying an antisense compound 8 to 30 nucleobases in length

targeted to a nucleic acid molecule encoding a human B7 protein to said individual; Claim 6 recites the method of claim 1, wherein said inflammatory skin disorder is psoriasis, Claim 8, recites the method of claim 1, wherein said human B7 protein is human B7-1 protein, claim 9 recites wherein said human B7 protein is human B7-2 protein. Claim 10 recites the method of claim 1, wherein said antisense compounds are targeted to both B7-1 and B7-2 proteins and is topically delivered.

In a preferred embodiment, Stinchcomb et al. teach a method for the treatment of autoimmune diseases, inflammatory disorders and allergies by inhibition of B7-1, B7-2, B7-3, and CD40 (see col. 1, lines 12-15). In one specific embodiment autoimmune diseases include, for example, "psoriasis." (see col. 5, lines 15-20).

The invention of Stinchcomb et al. features the use of one or more nucleic acid-based techniques e.g. "enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups," to induce graft tolerance, to treat autoimmune diseases and to treat allergies by inhibiting the synthesis of B7-1, B7-2, B7-3, CD40 proteins, and other potential targets including ICAM-1 (see col. 5, line 66 through col. 6, line 6). Additionally, the ribozymes of Stinchcomb et al. include hammerhead ribozymes targeted to the B7-1 and B7-2 transcripts (see example 1, starting col. 13, line 41), wherein the typical hammerhead ribozyme is approximately 13 to 40 nucleotides in length (note Table I at col. 15, lines 36-37) and discloses a number of potential target sequences for hammerhead ribozymes within the human B7-1 and B7-2 transcripts (Tables II and VI).

Stinchcomb et al. further teach that the ribozymes may be delivered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. Administration of the ribozyme compositions may include, for example, local, topical, systemic, ocular, intraperiotoneal, oral, and aerosol inhalation (col. 12, lines 18-36)

Stinchcomb et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stinchcomb et al. (US Pat. No. 5,877,021) or Freeman et al. (US Pat. No. 5,942,607), either in view of Abramowicz et al. (WO 94/17773) and Cooper et al. (WO 93/24134 A1)

Claim 1 recites a method for treating an inflammatory skin disorder in an individual in need thereof, comprising topically applying an antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding a human B7 protein to said individual; claim 2 the method of claim 1 wherein said antisense compound is an antisense oligonucleotide; claim 3 recites the method of claim 2, wherein at least one covalent linkage in said antisense compound is a modified covalent linkage; claim 4, the method of claim 2 wherein said antisense compound

has a modified sugar; claim 5, the method of claim 2, wherein said antisense compound has a modified nucleobase. Claim 6 recites the method of claim 1, wherein said inflammatory skin disorder is psoriasis, claim 7 wherein said inflammatory skin disorder is contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular dermatitis, generalized exfoliative dermatitis or eczema. Claim 8, recites the method of claim 1, wherein said human B7 protein is human B7-1 protein, claim 9 recites wherein said human B7 protein is human B7-2 protein. Claim 10 recites the method of claim 1, wherein said antisense compounds are targeted to both B7-1 and B7-2 proteins. Claim 11 recites the method of claim 2, wherein said antisense compound is in a formulation; Claim 12 recites the method of claim 2, wherein said antisense compound comprises at least one lipophilic moiety. Claim 13 recites a pharmaceutical composition comprising an anti-inflammatory or immunosuppressive agent, antisense targeting nucleic acid encoding human B7-1 and B7-2, and a pharmaceutical carrier. Claim 14 recites a method of treating an inflammatory skin disorder comprising topically applying the composition of claim 13.

The invention of Stinchcomb et al. features the use of one or more nucleic acid-based techniques e.g. "enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups," to induce graft tolerance, to treat autoimmune diseases and to treat allergies by inhibiting the synthesis of B7-1, B7-2, B7-3, CD40 proteins, and other potential targets including ICAM-1 (see col. 5, line 66 through col. 6, line 6). In one specific embodiment autoimmune diseases include, for example, "psoriasis." (see col. 5, lines 15-20).

Stinchcomb et al. further teach that the nucleic acid inhibitors of B7-1 or B7-2 may be delivered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. Administration of the ribozyme compositions may include, for example, local, topical, systemic, ocular, intraperiotoneal, oral, and aerosol inhalation (col. 12, lines 18-36)

Freeman et al. teach the use of antisense oligonucleotides complementary to the B7-1 and B7-2 transcripts as a means of blocking B7-1 or B7-2 expression in B-lymphocytes. Freeman et al. disclose two specific oligonucleotides, each 17 nucleotides in length, for use as antisense inhibitors of B7-1 and B7-2 expression (col. 18, lines 34-50). Freeman et al. teach the use of antisense compounds to inhibit B7-1 and B7-2 expression by delivering them to cells for the purpose of blocking T cell activation, which should be useful in treating autoimmune diseases (col. 17, line 62 to col. 18, line 23).

Stinchcomb et al. and Freeman et al. do not teach antisense oligonucleotides of 8 to 30 nucleobases in length targeting human B7-1 and B7-2, comprising a modified covalent linkage, nucleobase, sugar moiety, or modified with a lipophilic moiety. Additionally, these references do not specifically teach and the use of these antisense compounds in a method for treating, contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular dermatitis, generalized exfoliative dermatitis or eczema. Moreover, neither reference explicitly discloses a pharmaceutical composition comprising an anti-inflammatory or immunosuppressive agent, an antisense compound targeting human B7-1 and B7-2, and a pharmaceutically acceptable carrier;

or a method for treating an inflammatory disorder comprising the use of this pharmaceutical composition.

Abramowicz et al. teach that interleukin-10 (IL-10) functions to block the expression of B7 and ICAM-1 on human monocytes (page 11, lines 8-11). Abramowicz et al. also teach the use of IL-10 to treat or prevent diseases or conditions associated with the activity of B7 and it's receptor CD28 (see page 12, lines 7-10). In one particular embodiment, Abramowicz teach the use of IL-10 (a B7 inhibitor and ICAM-1) for the treatment or prevention of diseases selected from (*inter alia)* atopic dermatitis, and chronic eczema (see page 56, lines 22-24).

Cooper et al. teach the use of oligomeric compounds for the treatment of diseases associated with cellular hyperproliferation. These diseases include, for example, psoriasis, chronic dermatitis, psoriasiform dermatitis, and atopic dermatitis (page 20, lines 8-12). The oligomeric compounds of Cooper et al. are preferably 8 to about 40 nucleosidyl units (page 9, lines 26-29). These oligomeric compounds have internucleosidyl linkages linking the nucleoside monomers and, thus, includes oligonucleotides, nonionic oligonucleoside alkyl- and arylphosphonate analogs, alkyl- and aryl-phosphonothioates, phosphorothioates or phosphorodithioate analogs of oligonucleotides, phosphoramidate analogs of oligonucleotides. The oligomeric compounds also include nucleoside/non-nucleoside polymers wherein the base, the sugar and the phosphorous moiety have been replaced or modified (pages 5-6). In addition, the oligomers of Cooper et al. may comprise conjugation partners such as intercalators, and lipophilic agents, which may further enhance the uptake of the oligomer, modify the interaction of the oligomer with the target sequence, or alter the pharmacokinetic distribution of the oligomer (page 6, line35 to page 7, line 5). Moreover, Cooper et al. teach that oligomers that

comprise substituents such as 2'-O-methylribose groups, various base modifications, and analogs of the phosphorous backbone, such as phosphorothioates, can increase resistance to nucleases (page 14, lines 24-27).

It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Stinchcomb et al. and Freeman et al. to make the instantly claimed invention, wherein said invention comprises a method for treating inflammatory skin disorders such as dermatitis and eczema, and wherein the method comprises topically applying an antisense compound 8 to 30 nucleobases in length comprising the base, sugar, covalent linkage, and lipophilic modifications taught by Cooper et al. Additionally, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the teachings of Freeman or Stinchcomb et al. to make a pharmaceutical composition comprising an immunosuppressive agent, oligonucleotide inhibitors of human B7-1 and B7-2 expression, and a carrier. One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides of Freeman et al. (or the antisense nucleic acid of Stinchcomb et al.) with the sugar, base, the internucleosidyl backbone modifications, and lipophilic agents of Cooper et al. since these modifications are disclosed as enhancing the cellular properties of oligomeric compounds comprising these modifications. Furthermore, the disclosure of Cooper et al. also provides motivation and an expectation of success for the use of modified antisense oligonucleotides of 8 to 40 nucleotides in length for the treatment of various inflammatory skin disorders including dermatitis and psoriasis. One of ordinary skill in the art would have been motivated to modify the methods of Stinchcomb et al. and Freeman et al. to comprise the treatment of conditions such

as atopic dermatitis, and eczema since the prior art (Abramowicz et al.) discloses that these conditions can be treated by administration of an inhibitor of B7 expression.

One of ordinary skill in the art would have been motivated to design a pharmaceutical composition comprising oligonucleotide inhibitors of ICAM-1 (i.e. an anti-inflammatory or immunosuppressive agent, see claim 13), B7-1, and B7-2 for the treatment of an inflammatory skin disorder, since the prior art clearly discloses that inhibitors of ICAM-1 and B7 activity would be useful in the treatment of inflammatory skin diseases such as atopic dermatitis and eczema (Abramowicz et al.). Additionally, Stinchcomb et al. describes the use of immunosuppressive agents such as cyclosporine, azathioprine, and anti-B7 antibodies for the treatment of allograft rejection (col. 3, lines 25-68), therefore these compounds are disclosed in the prior art as having similar functions.

Moreover, one of ordinary skill in the art would have been motivated to make a composition comprising an anti-inflammatory or immunosuppressive agent and inhibitors of B7 activity since they are disclosed in the prior art as comprising similar functional properties, particularly for the treatment of allograft rejection (Stinchcomb), and for use in the treatment of an inflammatory skin disorder as per the teachings of Abramowicz. Furthermore, as per MPEP § 2144.06 "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose." "[T]he idea of combining them flows logically from their having been individually taught in the prior art." MPEP § 2144.06.

Therefore, the invention as a whole would have been *prima facie* obvious over Stinchcomb et al. or Freeman et al., either in view of Abramowicz et al. and Cooper et al.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
April 7, 2003